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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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To protect your privacy, we mail first class without mentioning AIDS on the

in a short article published by the American Foundation for AIDS Research.

Access to NIH-Funded Research Information -- Public Comment Period to November 16, 2004.....

The U.S. National Institutes of Health has proposed making reports of NIH-funded research freely available six months after their commercial publication. We show why this proposal is a step forward but far from a solution to the problem. We also refer readers to a micropayment idea we developed that might ease some of the remaining problems.

Depression: Louganis and Allen to Speak at Forums in New York, and San Francisco Oct. 27

by John S. James

Diver Greg Louganis and actor Chad Allen spoke about their struggles with depression at a public forum in New York (at the LGBT center on October 11), and will speak again in San Francisco on October 27, to raise awareness of the problem in the gay community. Men who have sex with men may be three times as likely as others to experience depression in their lifetime. These forums are sponsored by Gay and Lesbian Medical Association, the Association of Gay and Lesbian Psychiatrists, and GlaxoSmithKline.

The San Francisco forum is Wednesday October 27, 2004, 7:00 p.m., at The San Francisco GLBT Community Center, 1800 Market St., San Francisco.

Comment: Why Depression Is More Important Than Generally Realized

I attended the New York program, which had about one hour for talks by the panelists,

and by a psychiatrist from St. Vincent's Hospital Medical Center who served as moderator; the other hour was for questions and comments from the audience and responses from the panelists. I had not realized how serious and widespread debilitating depression can be for many individuals and for the community. A very impressive informal community response developed, with members of the audience helping some of the questioners learn how to get the services they needed after the formal program had ended. At least 150 people showed up for this forum, despite only a couple days' notice; others might have been unable to get in because the room was full, even after extra chairs were set up.

Antidepressant drugs were not the focus of this program, and were only briefly mentioned as a tool that some people may need temporarily. Certain kinds of short-term psychotherapy, and social support from friends and others, were more important to the participants. This program was intended for reducing stigma and silence, allowing depression to be talked about so that people can get the support and medical treatment they need.

Background Note on Risks and Benefits of Antidepressant Drugs

Coincidentally and not present at the New York public forum, the current issue of *Nature Medicine* published a news feature on antidepressant drugs(1). This article clearly explained a problem that has been in the news recently, that antidepressants can increase the suicide risk for children (and maybe adults). This problem, well known among psychiatrists but not always among general practitioners, is that patients with major depression often have suicidal impulses but are too depressed to act on them. But antidepressants cause different symptoms to lift at different rates. "The psychomotor retardation is the first thing to go, existential sadness is the last thing to go," so there is a critical risk period when people have the energy to act on their suicidal thoughts and feelings.

That article also noted that it is difficult to design antidepressant drugs because nobody knows what depression is or what causes it. Also, there is no animal model, as depression is seen as something that happens only to humans.

But it is now becoming well known in the medical world that depression can seriously increase progression of HIV and other diseases directly through biological mechanisms (not only indirectly, such as by interfering with medication adherence or social support). Chronic anxiety also appears to greatly increase disease progression, probably through different biochemical pathways. Medical care for these mental conditions may reduce progression (we do not have definitive data yet). *AIDS Treatment News* has described new scientific findings on depression and HIV progression twice in the past year.(2,3)

This matter has not had the attention it deserves, because of a philosophical bias in Western culture toward seeing the "mental" world as a ghostly reality separate from the physical body. In fact, depression and anxiety exist as biochemical changes in the body. It is no surprise that evolution could produce a level of anxiety that is unhealthy, because we needed fear to survive throughout human development. How the biochemistry of serious depression could be selected by evolution is much less clear, and a great diversity of theories has been proposed.

The immediate concern is that mental health care is usually the first to go when funding for medical treatment is cut. Also, if we understood how depression and anxiety (the biochemical changes that are most easily recognized by their mental effects) act to speed disease progression, we might find new mechanisms for pharmaceutical intervention to slow disease development and increase overall health.

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1. "Mood Swings," by A. Mandavilli. *Nature Medicine.* October 2004, volume 10, number 1-, pages 1210-1212.

2. "Chronically Depressed Women with HIV Almost Twice As Likely As Others to Die from AIDS-Related Causes; Those with Mental-Health Services Had Half the Death Rate of Those Without," by John S. James, http://www.aidsnews.org/2004/08/depressed-progression.html.

3. "'Shy' Study Suggests New Treatment Mechanism," by John S. James, http://www.aidsnews.org/2003/12/Shy.html.

New Fixed-Dose Once-a-Day Starting Regimens: Interview with Cal Cohen, M.D.

by John S. James

Dr. Cal Cohen is the research director of the Community Research Initiative of New England, teaches at Harvard Medical School in Boston, and is affiliated with Harvard Vanguard Medical Associates. Dr. Cohen spoke with *AIDS Treatment News* on September 10, 2004.

Background: On August 2, 2004, the FDA approved two fixed-dose combinations of previously approved drugs; both are dosed for once-daily use by adults. The FDA said that these combinations should be used together with at least one other antiretroviral not in the nucleoside/nucleotide class. In practice, they have been tested and used mostly with Sustiva (efavirenz), and with at least one (boosted) protease inhibitor as well.

The two new combinations are:

* Epzicom -- Ziagen (abacavir) + Epivir (3TC, lamivudine), and

* Truvada -- Viread (tenofovir) + Emtriva (FTC)

The studies cited below did not use the new combined pills, because they were not ready yet. They used the two separate drugs in the same doses.

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AIDS Treatment News: Recently the FDA approved two once-a-day fixed-dose combination pills -- Epzicom (Ziagen plus Epivir) from GlaxoSmithKline, and Truvada (Viread plus Emtriva) from Gilead Sciences. How do you see their use for patients who are first starting antiretrovirals?

Cal Cohen, M.D.: The fixed-dose combinations are primarily for convenience. The individual drugs were already approved in the U.S., and there is no medical reason that they had to be put into one pill. So the first decision is whether these are the right medicines for the patient.

The importance of fixed-dose combinations, and the reason there are now two more of them, is that several years ago, when AZT and 3TC were separate pills, Glaxo asked clinicians what they thought about putting them into one pill. As I recall, most of the doctors said that was not a priority, that their patients did not mind taking the extra pill. When Glaxo made Combivir anyway, its use was far greater than most physicians had predicted. Something about the simplicity was not anticipated, but was very important to many people taking these medicines. Maybe it was the one less co-pay, or one less bottle and refill to deal with. In any case the success of Combivir led to Trizivir (abacavir plus AZT plus 3TC), and now to these once-a-day combinations.

The issue of practicality and convenience is not to be minimized. But deciding which regimen you use is a choice of which meds you would pick, not just which fixed-dose combinations you would pick.

ATN: How do the once-a-day options compare with the twice-a-day antiretroviral treatments already in use?

Dr. Cohen: A head-to-head comparisons of Combivir vs. the same drug combination as Epzicom, presented in the fall of 2003 at the ICAAC conference, showed that the success of these regimens was spot-on identical. Sustiva was the 3rd drug in both cases.

The only differences were in side effects. With Epzicom, five to seven or eight percent of patients will have the hypersensitivity reaction to abacavir; this won't happen on Combivir. But there were other toxicities in favor of the Epzicom arm. For example, the CD4 counts went up higher on that arm than on the AZT-containing arm. There were fewer cases of nausea and vomiting, a well-known side effect of AZT. There was less anemia on Epzicom. Surprisingly there was a tiny bit more lipid increase on Epzicom than there was on Combivir. The significance of this difference is a subject of continued debate, but is just another factor to consider at this time.

So there is a series of tradeoffs -- hypersensitivity in some cases with Epzicom, vs. better CD4 counts and less hematologic toxicity than with Combivir.

ATN: What about Truvada?

Dr. Cohen: In as statement on August 26, 2004, Gilead released early (24 week) results of a study comparing the Truvada drugs with Combivir (the other drug was Sustiva in both cases). That study showed a difference in the overall intent-to-treat response rate, giving an 8% advantage to Truvada over Combivir. ["Intent to treat" analysis compares the total percent of volunteers who meet the study-defined success criterion after being assigned to take one drug vs. the other -- regardless of whether the others had drug failure due to viral rebound, had to stop that treatment due to side effects, or simply were lost to followup so that data was unavailable.]

The 24-week result was about 88% (on Truvada) vs. 80% (on Combivir) of the volunteers having a viral load of fewer than 400 copies. It seems that some if not most of this difference is explained by toxicity, as the researchers found more toxicity on the Combivir arm than on the Truvada arm. Drug discontinuation due to toxicity seems to be explaining most of the difference in the intent-to-treat analysis, but further details are needed to truly answer the question, and those presentations are anticipated at ICAAC this year [October 30 through November 2, 2004].

Truvada is better than Combivir in some ways, and you have other advantages with Epzicom. The head-to-head test of Truvada vs. Epzicom has not yet been done; it is being planned through the government-funded ACTG trials network.

So how do physicians choose between these two? Epzicom has five to eight percent chance of hypersensitivity, which while manageable certainly, is an issue to be dealt with in those starting the treatment. Clinicians need to review the symptoms of hypersensitivity with anyone starting abacavir in this or any combination – as it is not yet standard to try to predict who is in this five to eight percent. This extra step will be a consideration in deciding when to use this treatment, for some clinicians at least.

Truvada has none of the hypersensitivity; it is a relatively easy drug. It is certainly well tolerated; very low rates of discontinuation have been seen fairly consistently with Truvada regimen, as well as in all the studies of tenofovir and FTC separately. Those are both well-tolerated drugs, with very low rates of discontinuation for side effects or lab toxicity. And overall the virologic success rates have been excellent.

The few concerns about Truvada have been mainly issues around renal (kidney) toxicity and dosing. These drugs are cleared by the kidney, and for those with compromised kidney function, the doctor has to pay attention to accurate dosing, to not overdose the patient. And some people are asking, if these drugs are cleared by the kidney, does that mean we will see more renal toxicity?

Several physicians have presented studies of large cohorts of patients in their clinics, and so far one can safely conclude that while there are case reports of people who have had laboratory changes and decreases in renal function on tenofovir-based regimens, some very large cohorts have reassured us that these changes are rare events, and we

don't know how often they happen because of tenofovir, or at a rate different from other antiretrovirals. For example, in the head-to-head comparison of d4T vs. tenofovir, there was a very low rate of grade III renal problem on the d4T arm -- and yet people don't worry about d4T and renal toxicity. Just because there are case reports does not mean the tenofovir was involved. Most cohorts have been reassuring overall.

ATN: A statement on the labeling of tenofovir (at http://www.viread.com; see "Full prescribing Information," page 15 of the June 2004 version) noted slightly increased bone loss -- and suggested that supplementation with calcium and vitamin D might help with that.

Dr. Cohen: There has been much discussion for at least five years on tenofovir and bone loss. In both arms of the study, d4T and tenofovir, there was evidence of bone loss in the first year. It was about 1% more on tenofovir than d4t, but it happened in both arms. We don't usually think of d4T, 3TC, and Sustiva having a problem of bone loss. It was almost identical for men on tenofovir and men on d4T -- about 1% bone loss that stabilized after about one year. Only for women was the bone loss statistically worse for tenofovir.

So is this a tenofovir issue or an antiviral issue? The curves flatten out after a year -- bone loss for the first year, and then there seems to be stabilization for about two years [beyond that we don't have much data]. If this were a drug toxicity, we would generally expect it to get worse over time, not get worse for a year and then stabilize.

Could HIV be contributing to the bone loss? Some data suggests that people with HIV have bone loss even without taking antiretrovirals. If we look at what happened in the year before they started antiretrovirals, there is data to suggest bone loss from untreated HIV. So one possible explanation for what we are seeing is that the HIV-related bone loss may be continuing for the first year on treatment; not till year two is the control of HIV resulting in a slowing of bone loss. This does not explain the 1% difference in women on tenofovir vs. d4T. There may be some contribution of drug toxicity and another effect of drug benefit, in terms of long-term stability of people.

Whether that initial difference between tenofovir and d4t would be reversed by calcium supplementation is completely unanswered, at least from any public data sets. I am not aware that the bone loss is caused by the drug blocking calcium absorption in the gut. It would be an interesting study to see if calcium mattered or not. But for now it may be too simple to say bone loss happens and therefore calcium is the answer.

ATN: What about drug resistance with the new combinations?

Dr. Cohen: You don't have resistance too often with either of these starting regimens. But if you do, the choice is between tenofovir resistance and abacavir resistance (the percent of people who develop 3TC/FTC resistance is likely to be the same, based on these studies). There is no right or wrong answer; you don't want resistance to either one. Ultimately it is a tradeoff of other issues, since resistance to either abacavir or tenofovir causes cross-resistance to other medications in this class – and neither is a clear “winner” on this aspect.

If you look at the mutations, about 2 to 3 percent of patients who start treatment with tenofovir regimens will get the K65R mutation, and about the same percentage who start with abacavir regimens will get the L74V mutation. Both these mutations can cause cross-resistance to other nucleoside analogs.

One key issue that may be important in how often we see these mutations is how often people with very low CD4 counts were allowed in these studies. A fact some people are not aware of is that the Gilead trial did not have a lower CD4 cutoff -- you could have

zero and still be eligible. The abacavir trials had a lower cutoff of 50. It turns out this matters in terms of resistance. Most of those who developed mutations in the Gilead study had low CD4s when they entered. In fact, the single best predictor of who would develop tenofovir resistance was the CD4 at entry. The median CD4 count of those who developed the K65R tenofovir mutation was around 25 cells.

Therefore you cannot directly compare these studies, because they did not enroll people at the same risk of resistance. If you look just at those entering with CD4 above 50, there were very few in the tenofovir study who developed resistance.

Whether the correlation with CD4 at entry is medical or behavioral is hard to say. It could be behavioral -- if people who show up with that low a CD4 count are worse pill takers. Showing up with a CD4 count of 25 suggests that you are not actively pursuing health care in a preventive way. But it could also mean that the regimens may not be as protective at low CD4s as they are with less advanced disease, for biological reasons. We don't know the answer. We can observe that drugs work less well at very low CD4 counts, but don't know what explains this.

With these caveats, we now have a lot of confidence in Sustiva and two nucleosides. We have some differences in these regimens, and many similarities. Physicians are now gearing up to pick the one they think is best, given that treatment of HIV, at least in the U.S. and Europe, can be two pills once a day, with either fixed-dose combination you prefer. Overall I think that is wonderful.

The shorthand summary on which regimen (if one chooses one of these two once-a-day options) is that for some clinicians, it is a choice between the abacavir hypersensitivity story up front or not; they see this as a conversation that may leave patients feeling concerned about starting a medication that has that issue, rather than starting one that does not. That doesn't mean they won't use it. Sustiva's side effects, including vivid dreams and mood changes in many patients, have to be explained in either case. We are used to explaining the side effects of pills, but Truvada may have an easier starting conversation than Epzicom.

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2. Gilead press release, August 26, 2004: Gilead announces preliminary 24-week data from study 934 comparing Viread and Emtriva to Combivir both in combination with efavirenz in patients with HIV. http://www.gilead.com/wt/sec/pr_607254.

Warning Against Using Erythromycin (Even Orally) While Using Protease Inhibitors or Certain Other Drugs

An article in the September 9, 2004 *New England Journal of Medicine* reported that patients using the antibiotic erythromycin at the same time as drugs that strongly inhibited cytochrome P-450 3A (CYP3A, an enzyme in the liver that helps remove many drugs from the body) had an increased risk of sudden death from cardiac (heart) causes. But those who used amoxicillin, a different antibiotic, instead of erythromycin, did not have the problem. The authors concluded "concurrent use of erythromycin and strong inhibitors of CYP3A should be avoided."

The patients in this study were using oral erythromycin (not the injected form, which is probably more dangerous because of the

higher blood levels reached).

This study of Tennessee Medicaid recipients excluded those with HIV or other life-threatening conditions, so patients taking antiretrovirals were not included. But the mechanism of the drug interaction is well known (inhibition of the enzyme dangerously increases the erythromycin level, which can affect the heart rhythm) and it is clear that HIV protease inhibitors would also be a risk if used at the same time as the erythromycin.

In this study of medical records there were 194 person-years on erythromycin plus strong P-450 3A inhibitors at the same time, and three sudden deaths from cardiac causes. This is statistically significant, despite the small number of deaths, because none or one would have been expected.

Previous use of erythromycin in patients taking the enzyme inhibitors was also checked, and was not a problem. The dangerous blood levels occur when the drugs are used concurrently.

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Kaletra Monotherapy Controversy: AmfAR Publishes Overview

The November 2004 *HIV AIDS Treatment Insider* (published by the American Foundation for AIDS Research) has a short overview of the controversy around using Kaletra alone for HIV treatment for some patients -- mainly as an option for those who would otherwise have no antiretroviral treatment because they could not afford it. (1) A trial in Houston, Texas with 30 patients reported 48-week data at the big AIDS conference in Bangkok, Thailand in July.

The article, a fair presentation of both sides, also mentions other research plans for testing antiretroviral regimens with fewer than three drugs.

Note: The complete *HIV AIDS Treatment Insider* has two additional important articles: "Drug Pipelines May Flourish, But Not for HIV," by Kristen Kresge, and "Crunching the Numbers on Pharmaceuticals," by Elizabeth Paukstis. The complete issue can be read on the Web (or downloaded in PDF) at http://web.amfar.org/treatment/HIV+/insidermenu.asp.

References

(1) Monotherapy: An old strategy garners new interest, by Elizabeth Paukstis. *HIV AIDS Treatment Insider*; November 2004, volume 5, number 7, http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=133.

Access to NIH-Funded Research Information -- Public Comment Period to November 16, 2004

by John S. James

The U.S. National Institutes of Health is seeking public comment on a proposal for "establishing a comprehensive, searchable resource of NIH-funded research results and providing free access for all" -- but with important limitations. The proposal, summarized in a single page, is at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-064.html.

Basically, NIH plans to ask its grantees to submit a final manuscript to NIH after it has been peer reviewed, when it is accepted for publication. Six months after it is published (or sooner if the publisher agrees), NIH will publish it for free public access on its PubMed Central database, where it will be available without charge online.